Vitamin D, Infection, and Allergy

Carlos Camargo, MD, DrPH

Massachusetts General Hospital
Harvard Medical School
Boston, USA

November 4, 2011

Disclosure

Nothing to disclose

Objectives

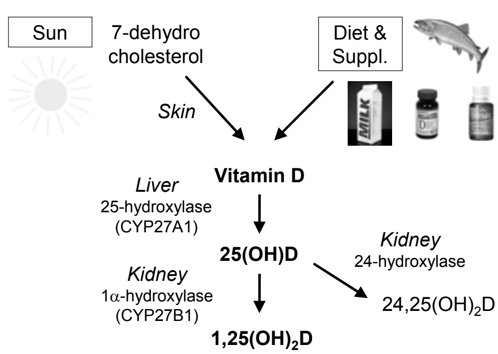
At the conclusion of this session, the participant should be able to:

- To identify main sources, clinical measurement, and general health effects of vitamin D
- To describe key studies on the association between vitamin D, infection, and allergy
- To discuss implications of recent vitamin D findings for allergy/immunology patients

Overview of Presentation

1. Vitamin D
2. Respiratory infections / wheezing
3. Asthma
   - Incident asthma
   - Exacerbations
4. Winter-related atopic dermatitis
5. Food allergy

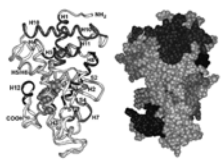
Vitamin D Synthesis & Metabolism



Severe Vitamin D Deficiency → Rickets

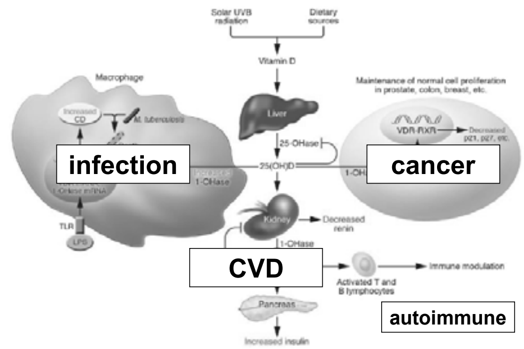
Vitamin D Receptor (VDR)

- VDR present in most tissues and cells of body
- Growing recognition that many different cells have the enzymatic machinery to convert 25(OH)D to the active hormone, $1,25(OH)_2D$
- >2,700 binding sites for VDR along genome
- Significant effects on activity of 229 genes



A. Norman, 2006; Ramagopalan, *Genom Res* 2010

Non-Calcemic Functions of Vitamin D



Holick, *J Clin Invest* 2006

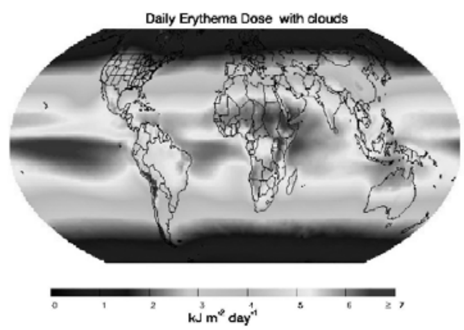


Figure 1. Global climatology (1979-1992) of mean daily erythemal (i.e., "sunburning") UV dose (from the NCAR web site http://www.acd.ucar.edu/TUV/).

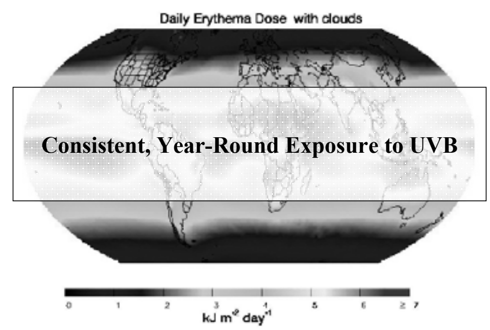


Figure 1. Global climatology (1979-1992) of mean daily erythemal (i.e., "sunburning") UV dose (from the NCAR web site http://www.acd.ucar.edu/TUV/).

Risk Factors for Vitamin D Insufficiency

- Winter at higher latitudes ✔ November - March
- Darker skin
- Lifestyle-related ↓ UVB exposure
  - Newborns with exclusive breastfeeding
  - Age 50+ (more indoors + ↓ skin conversion)
  - Sunscreen use
- Obesity (fat storage +)

Serum 25(OH)D *(cut-points vary by author)*

- Conversion factor: 1 ng/ml = 2.496 nmol/L
- Looking across multiple conditions, optimal level probably is ~40 ng/ml = ~100 nmol/L

Note: Some recommend 40-60 ng/ml

- Insufficiency: 10 – 29 ng/ml
- Deficiency: <10 ng/ml

2008 AAP: Defic <20 ng/ml
2011 IOM: Goal ≥20 ng/ml

Bischoff-Ferrari, *Osteopor Int* 2010; Canadian Paediatric Society 2007; Wagner, *Pediatrics* 2008; Institute of Medicine 2011

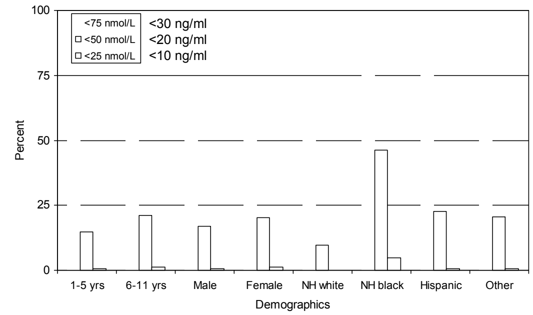
Institute of Medicine (IOM)

	1997		2011 *	
	AI	**Tol. UIL**	**RDA**	**ULI**
Birth to 12 months	200	1000	~400	<6m: 1000 6-12: 1500
Ages 1 to 70 years	1-50: 200 51-70: 400	2000	600	1-3: 2500 4-8: 3000 9-70: 4000
Age 71+ years	600		800	4000
Pregnant / lactating	200		600	

* Assumes minimal sunlight and target 25(OH)D ≥20 ng/ml

IOM 1997; IOM 2011

Low 25(OH)D Levels in US Children



Mansbach, *Pediatrics* 2009

Dietary Vitamin D → Serum 25(OH)D

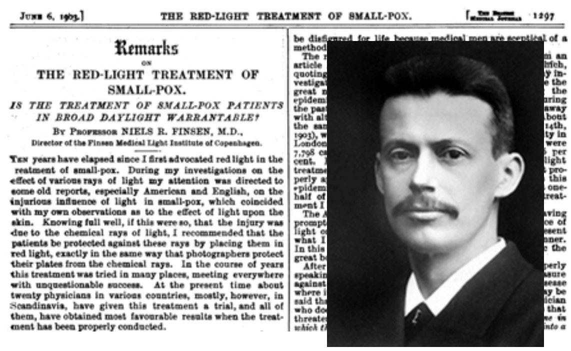
- Dietary intake has modest effect on 25(OH)D:
  - Glass of fortified milk (100 IU) = ↑ 1 ng/ml
  - 5 µg (200 IU) per day = ↑ 2 ng/ml
  - 10 µg (400 IU) per day = ↑ 4 ng/ml
  - 25 µg (1000 IU) per day = ↑ 10 ng/ml

typical MVI
200-600 IU

- Cod liver oil: *variable* (400 - 1300 IU per tbsp)
- Skin can create many <u>thousands</u> of IUs after only 15-20 minutes of direct UVB exposure

Multiple sources

Niels Finsen and Heliotherapy



June 6, 1903.] THE RED-LIGHT TREATMENT OF SMALL-POX.

Remarks
ON
THE RED-LIGHT TREATMENT OF SMALL-POX.

IS THE TREATMENT OF SMALL-POX PATIENTS IN BROAD DAYLIGHT WARRANTABLE?

By Professor NIELS R. FINSEN, M.D.,
Director of the Finsen Medical Light Institute of Copenhagen.

Ten years have elapsed since I first advocated red light in the treatment of small-pox. During my investigations on the effect of various rays of light my attention was directed to some old reports, especially American and English, on the injurious influence of light in small-pox, which coincided with my own observations as to the effect of light upon the skin. Knowing full well, if this were so, that the injury was due to the chemical rays of light, I recommended that the patients be protected against these rays by placing them in red light, exactly in the same way that photographers protect their plates from the chemical rays. In the course of years this treatment was tried in many places, meeting everywhere with unquestionable success. At the present time about twenty physicians in various countries, mostly, however, in Scandinavia, have given this treatment a trial, and all of them, have obtained most favourable results when the treatment has been properly conducted.

Finsen, *Br Med J* 1903

1903 Nobel Prize – UVR and Lupus Vulgaris

Heliotherapy for TB

Vitamin D and Epidemic Influenza

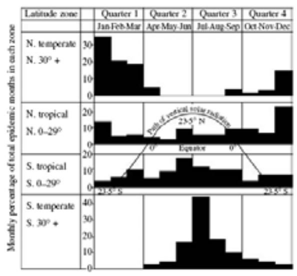
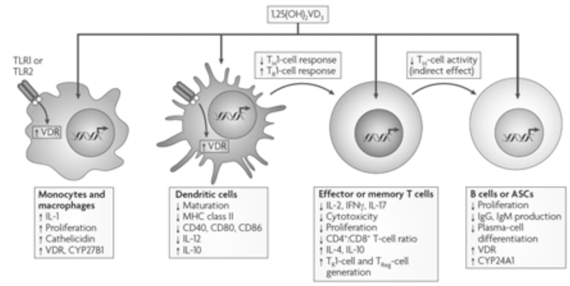


Fig. 1. The seasonal and latitudinal distribution of outbreaks of type A influenza in the world, 1964–1975,

"The nature of the seasonal stimulus remains undiscovered" (1981)

Hope-Simpson, *J Hygiene* 1981; Cannell, *Epidemiol Infect* 2006

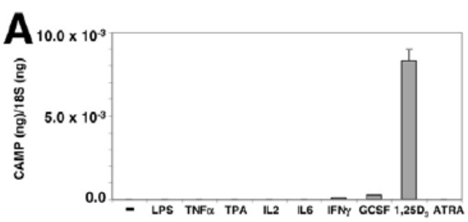
Immunologic Effects of Vitamin D



Mora, *Nature Rev Immunol* 2008

Cathelicidin Antimicrobial Peptide (CAMP)

Human CAMP gene is direct target of VDR and strongly up-regulated in myeloid cells by $1{,}25(OH)_2D3$

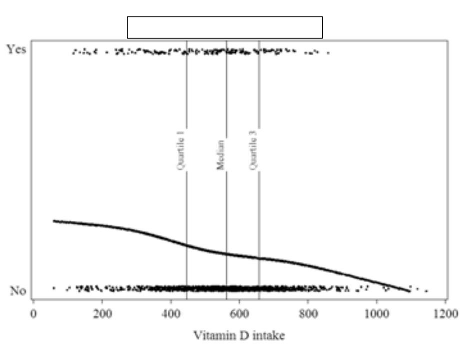


Gombart, *FASEB* 2005

Project Viva

- Based in Boston (northeastern USA)
- Prospective cohort study of ~2,000 pregnant women and their offspring (pre-birth cohort)
- *Objective*: To study pre- and peri-natal influences on outcomes of infancy, childhood, adulthood
- Data collection includes:
  - In-person visits (during pregnancy & childhood), with multiple interviews & questionnaires
  - Blood samples (frozen for future testing)

Maternal Vitamin D and Risk of Child Wheezing



Camargo, *Am J Clin Nutr* 2007

Published Cohort Studies (as of Dec 2010)

	Whz	Asth	Ecz	IgE	AR
Camargo, 2007 USA Maternal intake ... age 3y	↓		ns		
Devereux, 2007 Scotland Maternal intake ... age 5y	↓	ns		ns	
Erkkola, 2009 Finland Maternal intake ... age 5y		(↓)	ns		(↓)
Miyake, 2010 Japan Maternal intake ... age 2y	↓		↓		
Hypponen, 2004 Finland Infant supplement ... age 31y		↑		↑	↑
Gale, 2008 England Maternal 25(OH)D ...9m, 9y	(↑)	(↑)	(↑)		
Bäck, 2009 Sweden Infant supplement ... age 6y		composite ↑			

NZ Asthma & Allergy Cohort Study

- Based in New Zealand (PI: Julian Crane)
- Prospective cohort study of ~1,000 pregnant women and their offspring (birth cohort)
- *Objective*: To study peri-natal influences on asthma, allergies, and eczema
  - Cord blood 25(OH)D = median 18 ng/ml
  - Respiratory infection by age 3 months
  - Wheezing by age 5 years
  - Doctor-diagnosed asthma at age 5 years

Camargo, *Br J Nutr* 2010

Respiratory Infection By Age 3 Months

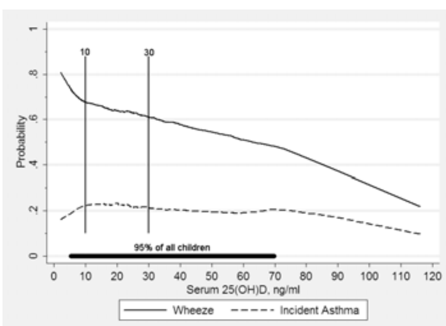
- Season-adjusted odds ratio (OR) was higher among those with low 25(OH)D:

30+ ng/ml:	1.00	
10-29:	**1.39**	(95%CI, 0.98-1.99)
<10:	**2.16**	(95%CI, 1.35-3.46)

- This inverse association was not materially changed by adjustment for 14 other factors

Camargo, *Pediatrics* 2011

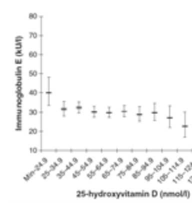
Cord Blood 25(OH)D, Wheeze, and Asthma



Camargo, *Pediatrics* 2011

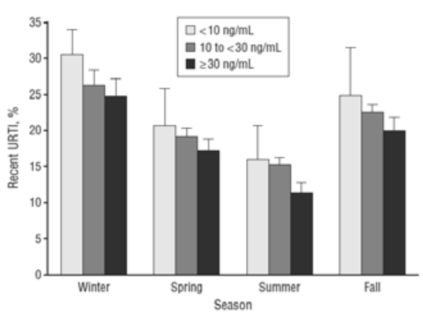
Curvilinear Association with IgE ?

- UK (Hyponnen, *Allergy* 2009):
  - Cross-sectional study, n=9377 adults, age 45y
  - Low & high 25(OH)D associated with higher levels of total IgE



- Arizona (Rothers, *JACI* 2011):
  - Birth cohort study, n=219 newborns → age 5 years
  - Low & high 25(OH)D associated with higher risk of aeroallergen sensitization

Vitamin D and Recent URI



Ginde, *Arch Intern Med* 2009

Randomized Trials on Respiratory Infection

- *Post hoc* analyses of bone RCTs suggest <u>benefit</u>
- First published RCTs (2009-2010)
  - New York (Li-Ng, *Epidemiol Inf* 2009): n=162 adults, 2000 IU/day x 3 mo: NS
  - Japan (Urashima, *Am J Clin Nutr* 2010): n=430 children, 1200 IU/day x 4 mo: P<0.05
  - Finland (Laaksi, *J Inf Dis* 2010) n=164 adults, 400 IU/day x 6 mo: P~0.05
  - Afghanistan (Manaseki-Holland, *Trop Med Int Health* 2010) n=224 children with pneumonia, 100k IU bolus: P<0.05
- Several ongoing RCTs of likely relevance, including studies of pregnancy/infancy and in all age groups

Asthma Exacerbations

- Prospective cohort data suggest benefit
  - Childhood wheezing studies
  - USA (Brehm, *J Allergy Clin Immunol* 2010)
    n=1024 children, baseline 25(OH)D, 4 years: P=0.01
- First published RCTs (2010-2011)
  - Japan (Urashima, *Am J Clin Nutr* 2010):
    n=430 children, 1200 IU/day x 4 mo: P<0.05
  - Poland (Majak, *J Allergy Clin Immunol* 2011)
    n=48 children, 500 IU/day x 6 mo: P<0.01
- Several ongoing RCTs, including studies of COPD

Asthma Severity & CS Response

- 54 adults + 100 children with asthma:
  cross-sectional analyses + *in vitro* testing
- Mean 25(OH)D = 28 + 31 ng/ml
- Higher serum 25(OH)D levels were associated with:
  - Better lung function (both)
  - Reduced airway hyper-responsiveness (adults)
  - Less corticosteroid use & fewer positive SPTs (children)
  - Improved *in vitro* response to corticosteroids (both)
- Vitamin D supplementation *may* improve multiple parameters of asthma severity & treatment response.

Sutherland, *AJRCCM* 2010; Searing, *JACI* 2010

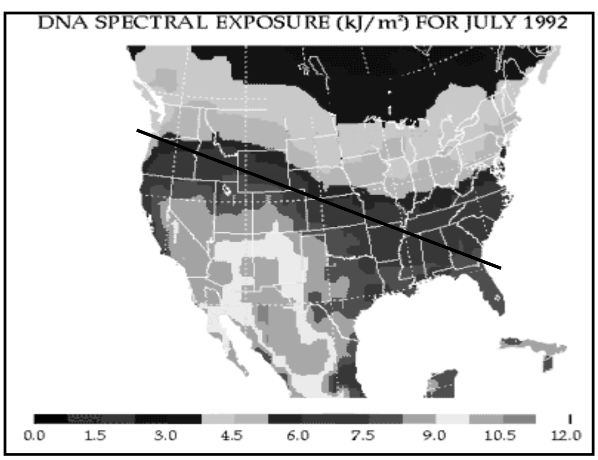
Skin – Norwegian RCT of Heliotherapy

- Health Ministry – “Health Travels” program
- Children with severe atopic dermatitis (AD) were randomly assigned to:
  - Visit Gran Canary Island for 4 weeks
  - Stay at home in Norway
- Improvement in all AD outcomes, including:
  - ↓ AD severity score
  - ↓ skin colonization by *S. aureus*
- No mention of vitamin D

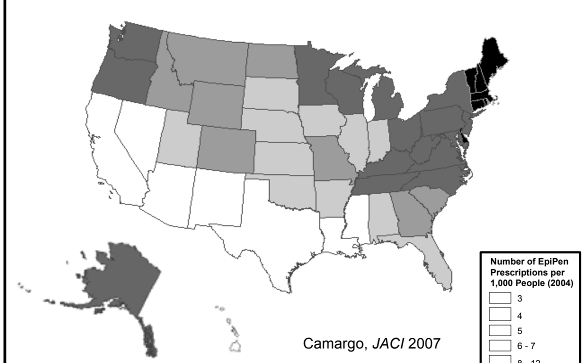
Byremo, *Allergy* 2006

Randomized Trials on Winter-related AD

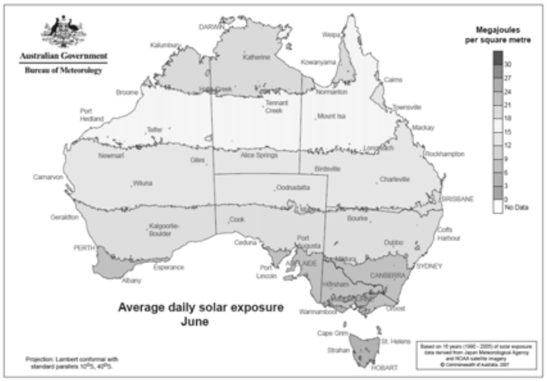
- Boston (Sidbury, *Br J Dermatol* 2008)
  - Pilot RCT of vitamin D supplement (1000 IU x 1 mo) vs. placebo; n=11 children
  - Vitamin D appeared to improve AD severity
- Mongolia (presented at 2009 WCPD, Bangkok)
  - clinicaltrials.gov NCT00879424
  - RCT of vitamin D supplement (1000 IU x 1 mo) vs. placebo; n=107 children
  - Vitamin D improved AD severity (p<0.05)
- Mediated by ↓ bacterial colonization of skin (?)



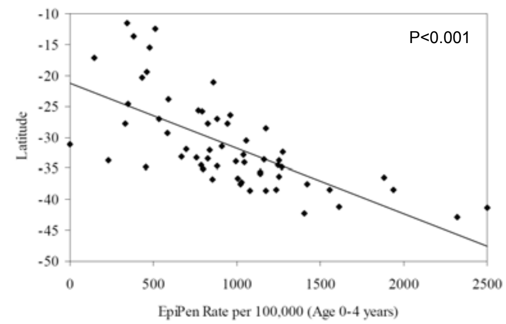
EpiPen Prescriptions per 1,000 State Residents



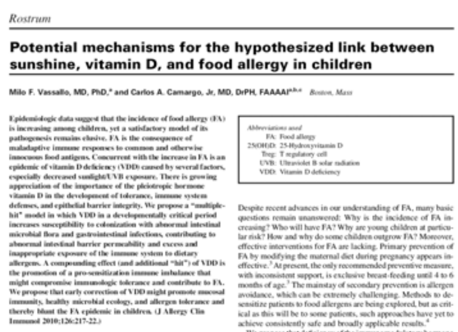
Camargo, *JACI* 2007



EpiPen Rx in Australia



Mullins, *Ann Allergy Asthma Immunol* 2009



Rostrum

Potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children

Milo F. Vassallo, MD, PhD,[a] and Carlos A. Camargo, Jr, MD, DrPH, FAAAAI[a,b,c] *Boston, Mass*

Epidemiologic data suggest that the incidence of food allergy (FA) is increasing among children, yet a satisfactory model of its pathogenesis remains elusive. FA is the consequence of maladaptive immune responses to common and otherwise innocuous food antigens. Concurrent with the increase in FA is an epidemic of vitamin D deficiency (VDD) caused by several factors, especially decreased sunlight/UVB exposure. There is growing appreciation of the importance of the pleiotropic hormone vitamin D in the development of tolerance, immune system defenses, and epithelial barrier integrity. We propose a "multiple-hit" model in which VDD in a developmentally critical period increases susceptibility to colonization with abnormal intestinal microbial flora and gastrointestinal infections, contributing to abnormal intestinal barrier permeability and excess and inappropriate exposure of the immune system to dietary allergens. A compounding effect (and additional "hit") of VDD is the promotion of a pro-sensitization immune imbalance that might compromise immunologic tolerance and contribute to FA. We propose that early correction of VDD might promote mucosal immunity, healthy microbial ecology, and allergen tolerance and thereby blunt the FA epidemic in children. (J Allergy Clin Immunol 2010;126:217-22.)

Abbreviations used
FA: Food allergy
25(OH)D: 25-Hydroxyvitamin D
Treg: T regulatory cell
UVB: Ultraviolet B solar radiation
VDD: Vitamin D deficiency

Despite recent advances in our understanding of FA, many basic questions remain unanswered: Why is the incidence of FA increasing? Who will have FA? Why are young children at particular risk? How and why do some children outgrow FA? Moreover, effective interventions for FA are lacking. Primary prevention of FA by modifying the maternal diet during pregnancy appears ineffective.[2] At present, the only recommended preventive measure, with inconsistent support, is exclusive breast-feeding until 4 to 6 months of age.[3] The mainstay of secondary prevention is allergen avoidance, which can be extremely challenging. Methods to desensitize patients to food allergens are being explored, but as critical as this will be to some patients, such approaches have yet to achieve consistently safe and broadly applicable results.[4]

Vassallo & Camargo,
JACI 2010

Population-based RCTs (as of Sept 2011)

- ViDA (Scragg & Camargo)
  - 5,100 men + women, age 50-84
  - Vit D_3 100,000 IU/month (equals ~3,300 IU/day)
  - Primary outcomes: CVD, infection, fractures ...
  - Enrollment started 2011 → results in 2017
- VITAL (Manson)
  - 20,000 subjects (men age 50+, women age 55+)
  - 2x2 factorial: 2000 IU/d Vit D_3 + 1 g/d EPA+DPA
  - Primary outcomes: cancer, CVD ...
  - Enrollment started 2011 → results in 2017

Summary & Clinical Implications

- Low 25(OH)D levels are associated with:
  - ↑ respiratory infections = ↑ wheezing & asthma exacerbations
  - *Possible* ↓ corticosteroid responsiveness
  - No association with incident childhood asthma
  - Winter-related atopic dermatitis
  - *Possible* ↑ risk of incident food allergy
- Emerging data from RCTs support <u>benefit</u> for infection
- Safety of high doses in pregnancy & infancy uncertain
  (possible ↑ allergy risk ... then traditional concerns re: ↑ calcium)
- Further research is needed, especially RCTs
- *My best guess?* Aim for serum 25(OH)D ~40 ng/ml